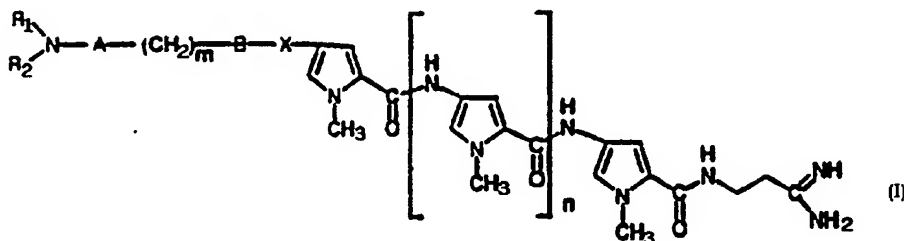




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(54) Title: NOVEL DISTAMYCIN ANALOGUES



(57) Abstract

Described are pyrrol-amidinic compounds of general formula (I) and their pharmaceutically acceptable salts, processes for their preparation and pharmaceutical compositions containing them, useful as antitumoral.

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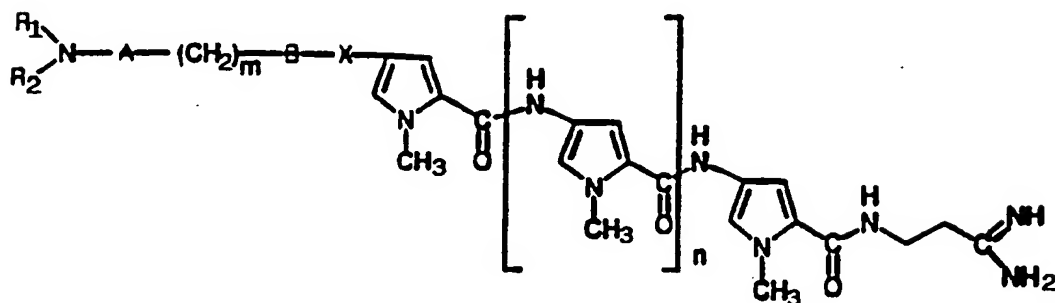
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NOVEL DISTAMYCIN ANALOGUES

Field of the invention

- 5 The present invention refers to pyrrol-amidinic compounds of general formula (I)



(I)

and their pharmaceutically acceptable salts wherein :

n is 0 or an integer ranging from 1 to 4

m is 0 or an integer ranging from 1 to 4

- 10 A is selected from the group consisting of : acyclic, aromatic or heterocyclic residue

B is selected from the group consisting of : a simple chemical bond, $-CO-NH-CH(R_3)-$, $-NH-CO-CH(R_3)-$ wherein R_3 is H or the side chain of a natural alpha-aminocarboxylic acid;

- 15 X is selected from the group consisting of : $-NHCO-$, $-CONH-$ and

wherein :

- i) R_1 and R_2 are equal and are selected from the group consisting of : oxiranomethyl, 1-aziridinomethyl, C_{2-4} alkyl optionally substituted in position 2 with an OH, C_{2-4} alkoxy, halogen or $-OSO_2R_4$ group wherein R_4 is selected from the group consisting of C_{1-4} alkyl or phenyl

or

- ii) $R_1 = H$ and R_2 is as above described

provided that :

- when $B = \text{chemical bond}$, n is different from 1

when $X = -CONH-$, $B = \text{simple chemical bond}$ and $m = 0$, n is different from 0

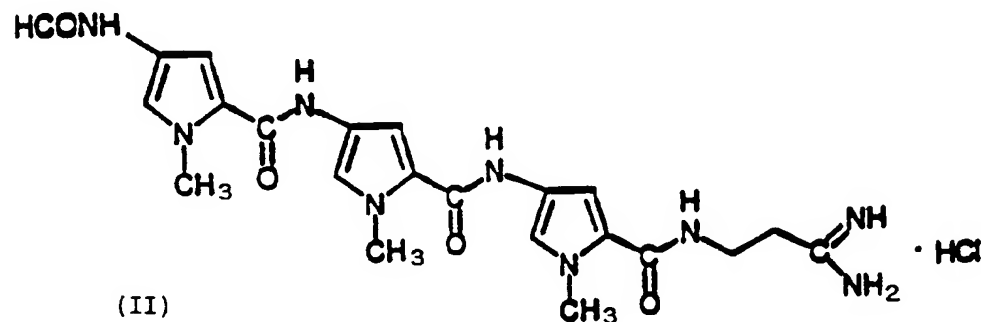
when $B = -CO-NH-CH(R_3)-$ X is different from $-NHCO-$

when $B = -NH-CO-CH(R_3)-$ X is different from $-CONH-$

- Furthermore the invention relates to processes for the preparation of the above mentioned compounds, to their pharmacologically active salts and to pharmaceutical compositions containing them.

Prior art

Antibiotic dystamicine is a known compound of formula (II) :



belonging to the pyrrol-amidinic group and showing interesting antiviral activity, for example against the herpetic viruses and Moloney sarcoma virus, is characterized by the ability to interact reversibly and selectively with DNA sequences rich in dA and dT
5 bases thereby interfering both in the replication and transcription process [see Arcamone in B. Pullman and J. Jorterez (eds) "Molecular basis of specificity in nucleic acid - drug interaction" 369-383, 1990 Kluwer Academic Publishers].

As is known, antiviral and antitumoral agents nowadays used in
10 therapy are characterized by serious side effects, limiting their use in a large number of cases which on the contrary should take advantage from the therapy; moreover therapeutical progresses are necessary in the clinical treatment of important solid tumors, as for example pulmonary tumors and ovarian tumors, not responding
15 adequately to any treatment nowadays in use.

A requisite for the therapeutic progress in this particular field is therefore the discovery of compounds having molecular moieties allowing them to increase the selectivity in inhibiting viral proliferation and the proliferation of tumoral rather than healthy
20 cells.

Detailed description of the invention

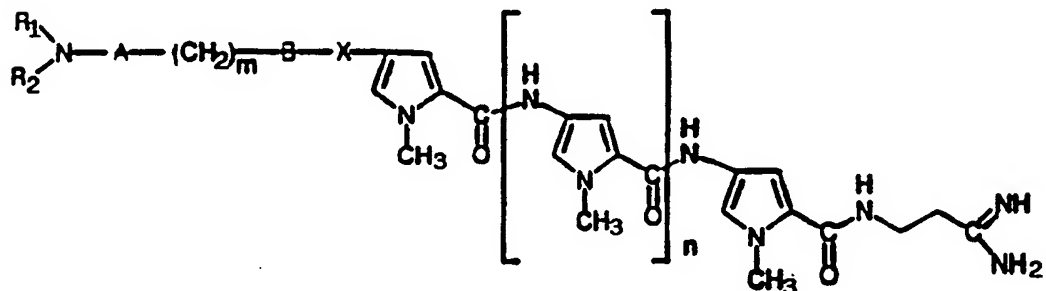
The present invention has the aim to render available new antitumoral and antiviral compounds and in particular compounds analogous to dystamicine containing new chemical modifications at

the N-terminal side chain level, and/or containing a different number of pyrrolic residues if compared to the natural product.

These compounds, show a marked antitumoral and antiviral activity, as well selectivity in the inhibition of tumoral cells and viruses

5 with respect to the healthy cells.

The compounds according to the present invention are those of general formula (I)



(I)

wherein:

n, m, A, B, X, R₁, R₂ are as previously described, and their
10 pharmaceutically acceptable salts.

Besides, the invention, refers to pharmaceutical compositions containing the above mentioned compounds, or pharmaceutically acceptable salts thereof formed with inorganic acids such as hydrochloric, hydrobromic, sulfuric, nitric and the like or with
15 organic acids such as acetic, propionic, succinic, malonic, citric, tartaric, methansulfonic, p-toluensulfonic and the like.

According to the present invention, preferred are the compounds of formula (I) wherein:

n is as above defined

m is zero or an integer comprised between 1 and 3.

5 A = cyclohexyl, p-phenylene, 1-methylpyrrole, thiophene, thiazole, imidazole, furan, isoxazole, oxazole, triazole, pyridine, pyrrole.

B is a simple bond, or when it is a -CO-NH-CH(R₃)- group or a -NH-CO-CH(R₃)- group, R₃ is preferably methyl, isobutyl, sec-butyl,

hydroxymethyl, mercaptomethyl, carbamoylmethyl, benzyl, 4-
10 hydroxybenzyl, 5-imidazolylmethyl, 2-carbamoylethyl, 2-methylthioethyl, 1-hydroxyethyl, 3-guanidinopropyl, 4-aminobutyl R₁ and R₂ represent preferably an ethyl group, 2-hydroxyethyl, 2-chloroethyl, methansulfonylethyl.

The following compounds are particularly preferred:

15 3-[1-Methyl-4-[1-methyl-4-[4-[N,N-bis(2-chloroethyl)amino]benzene-aminocarbonyl]pyrrol-2-carboxyamido]pyrrol-2-

carboxyamido]propionamidine hydrochlorate;

3-[1-Methyl-4-[1-methyl-4-[1-methyl-4-[1-methyl-4-[4-[N,N-bis(2-chloroethyl) amino]benzeneaminocarbonyl]-pyrrol-2-carboxyamido]

20 pyrrol-2-carboxyamido]pyrrol-2-carboxyamido]pyrrol-2-carboxyamido]

propionamidine hydrochlorate;

3-[1-Methyl-4-[1-methyl-4-[1-methyl-4-[1-methyl-4-[1-methyl-4-[4-[N,N-bis(2-chloroethyl)amino]benzeneaminocarbonyl]pyrrol-2-

carboxyamido]pyrrol-2-carboxyamido]pyrrol-2-carboxyamido]pyrrol-2-

25 carboxyamido] pyrrol-2-carboxyamido]propionamidine hydrochlorate;

3-[1-Methyl-4-[1-methyl-4-[4-[N,N-bis(2-chloroethyl)amino]benzene
butanamido]pyrrol-2-carboxyamido]pyrrol-2-carboxyamido]propiona-
midine hydrochlorate;

3-[1-Methyl-4-[1-methyl-4-[1-methyl-4-[1-methyl-4-[4-[N,N-bis(2-
5 chloroethyl)-amino]benzenbutanamido]pyrrol-2-carboxyamido]pyrrol-2-
carboxyamido]pyrrol-2-carboxyamido]pyrrol-2-
carboxyamido]propionamidine hydrochlorate;

3-[1-Methyl-4-[1-methyl-4-[1-methyl-4-[1-methyl-4-[1-methyl-4-[N,N-
bis(2-chloroethyl)amino]benzenebutanamido]pyrrol-2-carboxyamido]
10 pyrrol-2-carboxyamido]pyrrol-2-carboxyamido] pyrrol-2-carboxyamido]
pyrrol-2-carboxyamido]propionamidine hydrochlorate;

3-[1-Methyl-4-[1-methyl-4-[4[N,N-bis(2-chloroethyl)amino]benzyl-
amino carbonyl]pyrrol-2-carboxyamido]pyrrol-2-
carboxyamido]propionamidine hydrochlorate;

3-[1-Methyl-4-[1-methyl-4-[1-methyl-4-[1-methyl-4-[4-[N,N-bis(2
15 chloroethylamino)benzylaminocarbonyl]pyrrol-2-carboxyamido]pyrrol-2-
carboxyamido]pyrrol-2-carboxyamido]pyrrol-2-carboxyamido]propiona-
midine hydrochlorate;

3-[1-Methyl-4-[1-methyl-4-[2-[4-[N,N-bis(2-chloroethyl)amino)
20 phenyl] ethanaminocarbonyl]pyrrol-2-carboxyamido]pyrrol-2-carboxa-
mido] propionamidine hydrochlorate;

3-[1-Methyl-4-[1-methyl-4-[1-methyl-4-[1-methyl-4-[2-[4-[N,N-bis
(2-chloroethyl) amino]phenyl]ethanaminocarbonyl]pyrrol-2-carboxa-
mido]pyrrol-2-carboxyamido]pyrrol-2-carboxyamido]pyrrol-2-

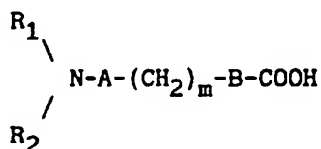
carboxyamido]propionamidine hydrochlorate;

3-[1-Methyl-4-[1-methyl-4-[1-methyl-4-[N,a-[4-[N,N-bis(2-chloro-ethyl)amino]benzoyl]glycylamino]pyrrol-2-carboxyamido]pyrrol-2-carboxyamido]pyrrol-2-carboxyamido]propionamidine hydrochlorate;

5 3-[1-Methyl-4-[1-methyl-4-[1-methyl-4-[1-methyl-4-[N,a-[4-[N,N-bis(2-chloroethyl)amino]benzoyl]glycylamino]-pyrrol-2-carboxyamido]pyrrol-2-carboxyamido]pyrrol-2-carboxyamido]pyrrol-2-carboxyamido]propionamidine hydrochlorate;

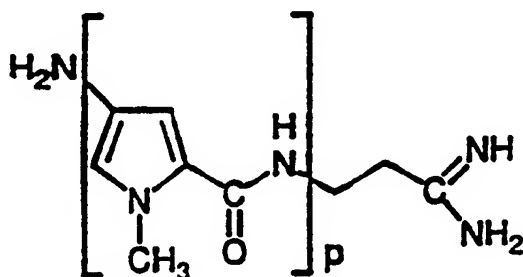
Compounds of general formula (I) can be prepared according to the
10 following processes:

a) reacting the compound of formula (III)



(III)

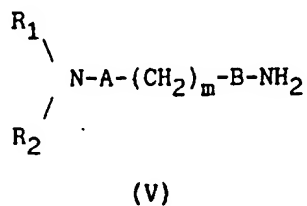
wherein B is a chemical bond or the $-CONHCH(R_3)-$ group wherein R_3 is as above defined, and m, A, R_1 and R_2 are as above defined, or a reactive derivative thereof, with a compound of formula (IV)



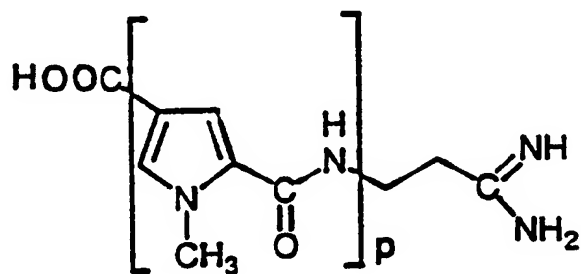
(IV)

wherein p is an integer comprised between 2 and 6, thereby obtaining the compounds of formula (I) wherein $X = -CONH-$, B is a chemical bond or the $-CO-NH-CH(R_3)-$ group and m , n , A , B , R_1 , R_2 and R_3 are as above defined;

- 5 a') reacting the compound of formula (V)

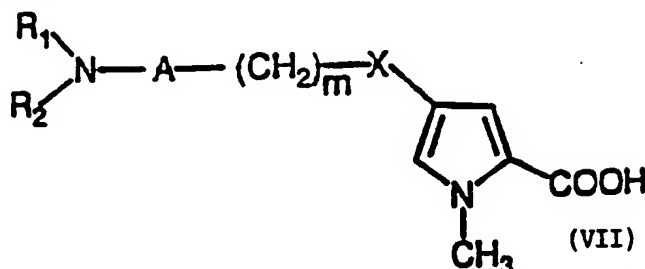


wherein B is a chemical bond or the $-NHCOCH(R_3)-$ group, wherein R_3 is as above defined, and m , A , R_1 and R_2 are as above defined, with a compound of formula (VI).

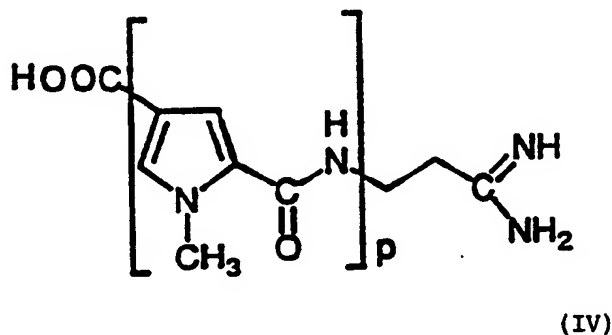


- wherein p is an integer comprised between 2 and 6, thereby
- 10 obtaining the compounds of formula (I) wherein $X = -NHCO-$, B is a chemical bond or the $-NH-CO-CH(R_3)-$ group and m , n , A , B , R_1 , R_2 and R_3 are as above defined;

b) reacting the compound of formula (VII)



wherein m , A , X , R_1 and R_2 are as above defined, with a compound of formula (IV)



wherein p is an integer comprised between 1 and 5, thereby
 5 obtaining the compounds of formula (I) wherein B is a chemical bond
 and m , n , A , X , R_1 and R_2 are as above defined.

The amidation reactions of the compound of formula (III) with a
 compound of formula (IV) wherein p is an integer comprised between
 2 and 6, of the compound of formula (V), wherein R_1 , R_2 , A , m and B
 10 are as previously defined, with the compound of formula (VI),
 wherein p is comprised between 2 and 6, and of the compound of
 formula (VII), wherein R_1 , R_2 , A , m , X are as above defined, with a
 compound of formula (IV) wherein p is an integer comprised between
 1 and 5, can be carried out in the presence of condensing agents as

DCC (dicyclohexylcarbodiimide) or EDC [1-dimethylaminopropyl)-3-ethylcarbodiimide hydrochlorate] and possibly in the presence of hydroxybenzotriazole or BOP (benzotriazol-1-iloxy(dimethylaminophosphoniumhexafluoride phosphate) or by using a
5 reactive derivative of the acids (III) and (IV) as for example an acylchloride, an acylimidazole, an acylazide or an active ester, such as 2,4,5 trichlorophenoxyester or N-oxy succinimidoester, or an anhydride thereof.

Preferably the above defined amidation reactions are carried out
10 using molar ratio of from 1:1 to 1:3 in an inert organic solvent as for example dimethyl sulfoxide, hexamethyl phosphotriamide, dimethylacetamide, or preferably dimethyl formamide in the presence of a condensing agent as above described and of N-hydroxybenzotriazole or BOP and in the presence of an organic base
15 as triethylamine, diisopropylethylamine and 1,8-bis(dimethylamino)-naphthalene.

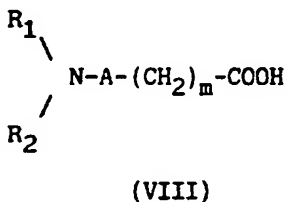
The reaction temperature may be comprised between -10 °C and 50 °C and the time required for the reaction ranges from 2 to 48 hours.

The reaction of the compound of formula (III) or the compound of
20 formula (VII) with the compound of formula (IV) may be carried out using a reactive derivative of the compound of formula (III) or of the compound of formula (VII) of the above mentioned type, and therefore accomplishing the reaction in a biphasic system water-organic solvent as Schotten-Baumann amidation or in an organic

solvent as for example a hydroxyde, a carbonate or a bicarbonate of an alkaline metal, preferably sodium, potassium, barium or an organic base as triethylamine, diisopropylamine, pyridine or N,N dimethylaminopyridine.

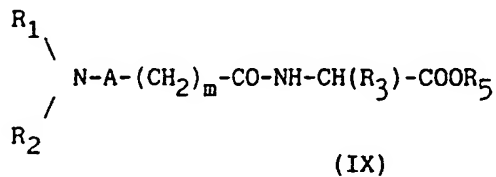
- 5 The reaction is usually conducted at room temperature and the time required for the reaction varies from 2 to 24 hours.

In the process (a), the compounds of formula (III) wherein B is a chemical bond and m, A, R₁ and R₂ are as above defined, namely the compounds of formula (VIII)



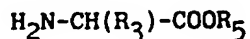
- 10 either are already commercially available or they are prepared by conventional processes of the organic chemistry, starting from known compounds as reported for example in J. Med. Chem. 32, 774 (1989) or J. Org. Chem. 26, 4996 or in J. Med. Chem. 33, 1177 (1990).

- 15 In the process (a) a compound of formula (III) wherein B is the group -CO-NH-CH(R₃)- and m, A, R₁, R₂ and R₃ are as above defined, can be prepared by the hydrolysis of the compounds of formula (IX)



wherein A, m, R₁, R₂, R₃ are as above defined and R₅ is a protecting group characteristic of the carboxylic group of aminoacids as methyl, ethyl, t-butyl, benzyl, trimethylsilyl, the hydrolysis of the compound of formula (IX) can be carried out following the known methods and processes of the organic chemistry as for example reported in T. W. Greene Protective groups in Organic Synthesis Wiley Interscience Publication 1981.

A compound of formula (IX) wherein A, m, R₁, R₂, R₃ and R₅ are as above defined, can be prepared by reacting a compound of formula (VIII) wherein A, m, R₁ and R₂ are as above defined or its reactive derivative with a compound of formula (X)



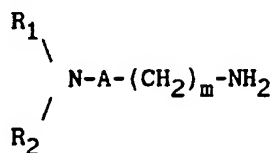
(X)

wherein R₃ and R₅ have the above defined meanings.

A reactive compound of an acid of formula (VIII) can be the same already reported in the present application for the compound of formula (III) or for the compound of formula (VII) and the reaction can be accomplished under similar conditions to those reported for the amidation reaction of a compound of formula (III) or a compound of formula (VII) with a compound of formula (IV).

The compounds of formula (X) either are commercially available or can be prepared by the conventional processes starting from the corresponding aminoacids as described for example in E. Gross, J. Meienhofer, The Peptides V. 3, p. 102-132, 1981, Academic Press.

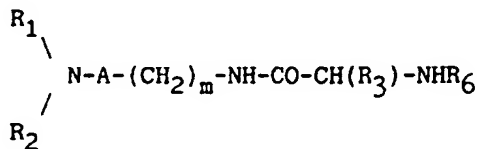
In the process (a') a compound of formula (V) wherein B is a chemical bond and m, A, R₁ and R₂ are as above defined, namely compounds of formula (XI)



(XI)

either are commercially available or are prepared by the
5 conventional processes of the organic chemistry as reported for example in J. Med. Chem. 33, 112 (1990).

In the process (a') a compound of formula (V) wherein B is the group -NHCOCH(R₃) wherein m, A, R₁, R₂ and R₃ are as above defined, can be prepared by hydrolysis of the compounds of formula (XII)

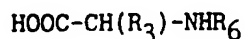


(XII)

10 wherein A, m, R₁, R₂, R₃ are as above defined and R₆ is a protecting group characteristic of the amino group of aminoacids as trifluoroacetyl, benzyloxycarbonyl, tertbutyloxycarbonyl, 9-fluorenylmethyloxycarbonyl and trityl, the hydrolysis of the compound of formula (XII) can be carried out following the methods
15 and processes known in the organic chemistry as for example reported in T. W. Greene Protective group in Organic Synthesis

Wiley Interscience Publication 1981.

A compound having formula (XII) wherein A, m, R₁, R₂, R₃ and R₆ are as above defined can be prepared by reacting a compound of formula (XI) wherein A, m, R₁ and R₂ are as above defined, with a compound
5 of formula (XIII)



(XIII)

wherein R₃ and R₆ are as above defined, or with its reactive derivative.

A reactive derivative of an acid of formula (XIII) can be the same as reported in this application for the compound having formula
10 (III) or for the compound having formula (VII) and the reaction can be carried out under similar conditions to those reported for the amidation reaction of a compound of formula (III) or a compound of formula (VII) with a compound of formula (IV).

The compounds of formula (XIII) either are commercially available
15 or are prepared by conventional procedures, starting from aminoacids as described for example in E. Gross, J. Meienhofer, The Peptides V. 3, p. 102-132, 1981, Academic Press.

In the process (b), a compound of formula (VII) wherein m, A, X, R₁ and R₂ are as above defined, can be prepared as described in the
20 International Patent application No. WO 93/13739 published on 22nd July 1993 in the name of the same applicant and herein reported by reference.

In the processes (a) and (b) a compound of formula (IV) either is a commercially available compound or can be prepared by the known methods [Gazzetta Chimica Italiana, 99, 632 (1969)].

In the process (a') a compound of formula (VI) can be prepared
5 according to the methods described in the International Patent application No. WO 93/13739 published on 22nd July 1993 in the name of the same applicant and herein reported by reference.

The compounds of the present invention have antitumoral and antiviral activity, in particular they show high cytotoxicity
10 levels against the tumoral cellular lines.

Moreover the present invention relates to pharmaceutical compositions comprising as active principle a compound of general formula (I) or a pharmaceutically acceptable salt thereof with a pharmaceutically acceptable vehicle or diluent.

15 A therapeutically effective amount of the compound of formula (I) according to the invention is combined with an inert and pharmaceutically acceptable vehicle. Conventional vehicles can be used and the compositions can be prepared using the conventional techniques. The compounds according to the present invention are
20 useful for human and animal therapeutical treatment.

In particular, the compounds according to the present invention are useful as antitumoral and / or antiviral agents when administered to patients in a therapeutically effective amount, for example a suitable dosage for the administration to adult patients can vary
25 from about 0.1 and 100 mg per unitary dose from one to 4 times a

day.

EXAMPLE 1

3-[1-Methyl-4-[1-methyl-4-[1-methyl-4-[4-[N,N-bis(2-chloroethyl)amino]benzenbutanamido]pyrrol-2-carboxyamido]pyrrol-2-carboxyamido]pyrrol-2-carboxyamido]propionamidine hydrochlorate

(I, X = -CONH-, A = p-phenylene, B = 0, m = 3, n = 2, R₁ = R₂ = 2-chloroethyl).

4-[Bis(2-chloroethyl)amino]benzenebutanoylchloride (801 mg, 2.49 mmols), (obtained by the corresponding carboxylic acid VIII, (A = p-phenylene, m = 3, R₁ = R₂ = 2-chloroethyl) (750 mg, 2.49 mmols) by treatment with SOCl₂ (1.2 ml) in tetrahydrofuran (25 ml) under reflux), are dissolved in 25 ml anhydrous tetrahydrofuran and added to a solution of 3-[1-Methyl-4-[1-methyl-4-[1-methyl-4-(1-methyl-4-aminopyrrole-2-carboxyamido)pyrrol-2-carboxyamido]pyrrol-2-carboxyamido]pyrrol-2-carboxyamido]propionamidine hydrochlorate (IV, p = 4) (327 mg, 0.51 mmols), [Gazzetta Chimica Italiana, 99, 632 (1969)] and sodium bicarbonate (90 mg, 1.11 mmols) in 40 ml water.

After one hour stirring at room temperature, the reaction mixture is evaporated to dryness and the residue is separated by chromatography on silica gel (eluent CHCl₃/MeOH 7/3) thus obtaining 276 mg I (X = -CONH-, A = p-phenylene, B = 0, m = 3, n = 2, R₁ = R₂ = 2-chloroethyl) (yield 60 %).

¹H-NMR (DMSO-d₆), d : 1.82 (m, 2H), 2.25 (t, 2H), 2.45 (t, 2H), 2.64 (t, 2H), 3.50 (m, 2H), 3.70 (s, 8H), 3.82 (s, 3H), 3.85 (s, 3H), 3.86 (s, 3H), 3.87 (s, 3H), 6.69 (d, 2H), 6.90 (d, 1H), 6.97 (d, 1H), 7.04 (d, 2H), 7.08 (bs, 2H), 7.15 (d, 1H), 7.18 (d, 1H), 7.22 (bs, 2H), 8.19 (t, 1H), 8.57 (bs, 2H), 8.95 (bs, 2H), 9.76 (s, 1H), 9.90 (m, 3H).

The following compound of formula (I) is also obtained by an analogous process:

10 3-[1-Methyl-4-[1-methyl-4-[4-[N,N-bis(2-chloroethyl)amino]benzene butanamido]pyrrol-2-carboxyamido]pyrrol-2-carboxyamido] propionamide hydrochlorate (I, X = -CONH-, A = p-phenylene, B = 0, m = 3, n = 0, R₁ = R₂ = 2-chloroethyl).

¹H-NMR (DMSO-d₆), d : 1.80 (m, 2H), 2.24 (t, 2H), 2.50 (t, 2H), 2.62 (t, 2H), 3.50 (m, 2H), 3.70 (s, 8H), 3.81 (s, 3H), 3.83 (s, 3H), 6.68 (d, 2H), 6.87 (d, 1H), 6.92 (d, 1H), 7.04 (d, 2H), 7.13 (d, 1H), 7.16 (d, 1H), 8.18 (t, 1H), 8.65 (bs, 2H), 8.94 (bs, 2H), 9.75 (s, 1H), 9.83 (s, 1H).

20

EXAMPLE 2

3-[1-Methyl-4-[1-methyl-4-[1-methyl-4-[1-methyl-4-[4-[N,N-bis(2-chloroethyl)amino]benzenaminocarbonyl]pyrrol-2-carboxyamido]pyrrol-2-carboxyamido]pyrrol-2-carboxyamido]pyrrol-2-carboxyamido] propionamide hydrochlorate

25 (I, X = -NHCO-, A = p-phenylene, B = 0, m = 0, n = 2, R₁ = R₂ = 2-

chloroethyl).

(337 mg, 0.84 mmoles) of 1-Methyl-4-[4-[N,N-bis(2-chloroethyl)-amino]benzenaminocarbonyl] pyrrol-2-carboxylic acid chloride (VII, A = p-phenylene, X = -NHCO-, m = 0, R₁ = R₂ = 2-chloroethyl),
55 (obtained by treatment of the carboxylic acid VII (A = p-phenylene, X = -NHCO-, m = 0, R₁ = R₂ = 2-chloroethyl) (322 mg, 0.84 mmoles) with SOCl₂ (4.2 mmoles) dissolved in CH₂Cl₂ and in the presence of dimethylformamide), are dissolved in 10 ml tetrahydrofuran and added to a mixture of N-deformyldystamine (221 mg, 0.42 mmoles)
10 and diisopropylethylamine (0.3 ml, 2.1 mmoles) in anhydrous EtOH (5 ml).

The mixture is maintained 30 minutes under stirring at room temperature, then ethylacetate is added up to the precipitation of the raw product, which after separation by HPLC (H₂O/CH₃CN/CF₃COOH
15 56/44/0.1) gives 162 mg of I (X = -NHCO-, A = p-phenylene, B = 0, m = 0, n = 2, R₁ = R₂ = 2-chloroethyl). (yield 45 %).

¹H-NMR (DMSO-d₆). δ : 2.60 (t, 2H), 3.50 (m, 2H), 3.70 (s, 8H), 3.81 (s, 3H), 3.86 (s, 3H), 3.88 (s, 3H), 3.92 (s, 3H), 6.74 (d, 2H), 6.96 (d, 1H), 7.08 (s, 2H), 7.18 (d, 2H), 7.25 (d, 1H), 7.28 (d, 1H), 7.42 (d, 1H), 7.54 (d, 2H), 7.69 (d, 1H), 8.17 (t, 1H), 8.50 (bs, 2H), 8.59 (bs, 2H), 9.49 (s, 1H), 9.88 (s, 1H), 9.94 (s, 1H), 10.09 (s, 1H).

The following compound of formula (I) is also obtained by an

analogous process:

3-[1-Methyl-4-[1-methyl-4-[1-methyl-4-[1-methyl-4-[4-
[N,N-bis(2-chloroethyl)amino]benzenaminocarbonyl]pyrrol-2-
carboxyamido]pyrrol-2-carboxyamido]pyrrol-2-carboxyamido]pyrrol-2-
5 carboxyamido]pyrrol-2-carboxyamido] propionamidine hydrochlorate
(I, X = -NHCO-, A = p-phenylene, B = O, m = 0, n = 3, R₁ = R₂ = 2-
chloroethyl).

¹H-NMR (DMSO-d₆), d : 2.60 (t, 2H), 3.50 (m, 2H), 3.70
(s, 8H), 3.81 (s, 3H), 3.85 (s, 3H), 3.87 (s, 6H), 3.92
10 (s, 3H), 6.72 (d, 2H), 6.95 (d, 1H), 7.07 (m, 3H), 7.16
(d, 1H), 7.21 (d, 1H), 7.23 (d, 1H), 7.26 (d, 1H), 7.41(d,
1H), 7.52 (d, 2H), 7.68 (d, 1H), 8.18 (t, 1H), 8.47 (bs,
2H), 8.89 (bs, 2H), 9.48 (s, 1H), 9.88 (s, 1H) 9.90
(s, 1H), 9.93 (s, 1H), 10.09 (s, 1H)

15 EXAMPLE 3

N-[4-[N,N-bis(2-chloroethyl)amino]benzoyl]glycine (III, A = p-
phenylene, m = 0, R₁ = R₂ = 2-chloroethyl, B = -CONHCH(R₃)-, R₃ =
H)

A mixture composed by glycine (600 mg, 8 mmoles),
20 bis(trimethylsilyl)acetamide (3.25 g, 16 mmoles), and
trimethylsilylchloride (0.2 ml, 1.6 mmoles) in CH₂Cl₂ (20 ml) is
kept under reflux for 2 hours.

After cooling to room temperature, (3 g, 10.8 mmoles) of 4-[N,N-
bis(2-chloroethyl)amino]benzoylchloride are added to the reaction

mixture, which is maintained under stirring at 40 °C.

After 2 hours, the mixture is acidified with 1N HCl and extracted with CH₂Cl₂; the organic extracts are collected and extracted on their turn with an aqueous solution of NaHCO₃, and the basic phase,

5 after acidification with 1N HCl is extracted with CH₂Cl₂ thus obtaining after evaporation of the organic phase, 1.32 g of III (A = p-phenylene, m = 0, R₁ = R₂ = 2-chloroethyl, B = -CONHCH(R₃)-, R₃ = H), (yield 52 %)

¹H-NMR (DMSO-d₆), δ : 3.78 (m, 8H), 3.88 (d, 2H), 6.78

10 (d, 2H), 7.72 (d, 2H), 8.46 (t, 1H).

EXAMPLE 4

3-[1-Methyl-4-[1-methyl-4-[1-methyl-4-[N,a-[4-[N,N-bis(2-chloroethyl)amino]benzoyl]glycylamino]pyrrol-2-carboxyamido]pyrrol-2-carboxyamido]pyrrol-2-carboxyamido]propionamidine hydrochlorate

15 (I, X = -CONH-, A = p-phenylene, B = -CONHCH(R₃)-, R₃ = H, m = 0, n = 1, R₁ = R₂ = 2-chloroethyl).

308 mg (0.58 mmoles) N-deformyldystamicine, 136 mg (1 mmole) N-hydroxybenzotriazole (HOBT), 182 mg (0.85) mmoles 1.8-bis-(dimethylamino)-naphthalene and 191 mg (0.11 mmoles) [1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (EDC) are added to a

20 solution of 270 mg, (0.85 mmoles) III (A = p-phenylene, m = 0, R₁ = R₂ = 2-chloroethyl, B = -CONHCH(R₃)-, R₃ = H), prepared as described in example 3 and dissolved in anhydrous dimethylformamide (45 ml).

25 The reaction mixture is maintained under stirring at room

temperature for one hour, then ethylacetate is added up to precipitation of the raw product, which after chromatography on silica gel (eluent $\text{CH}_2\text{Cl}_2/\text{anhydrous EtOH}/\text{H}_2\text{O}$ 65/35/2) gives 275 mg of I ($X = -\text{CONH}-$, $A = p\text{-phenylene}$, $B = -\text{CONHCH}(\text{R}_3)-$, $\text{R}_3 = \text{H}$, $m = 0$,

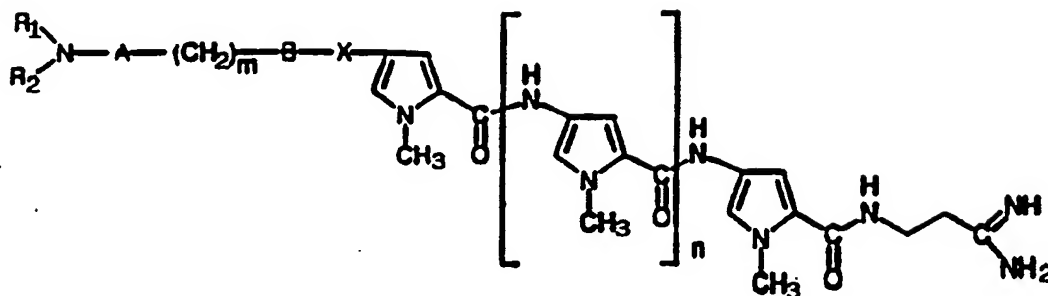
5 $n = 1$, $\text{R}_1 = \text{R}_2 = 2\text{-chloroethyl}$) (yield 60 %)

$^1\text{H-NMR}$ (DMSO-d_6). δ : 2.64 (t, 2H), 3.50 (m, 2H), 3.78 (s, 8H), 3.82 (s, 3H), 3.84 (s, 6H), 3.97 (d, 2H), 6.78 (d, 2H), 6.91 (s, 2H), 7.04 (d, 1H), 7.14 (d, 1H), 7.18 (d, 1H), 7.21 (d, 1H), 7.78 (d, 2H), 8.21 (t, 1H), 8.52

10 (t, 1H), 8.78 (bs, 2H), 9.04 (bs, 2H), 9.89 (s, 2H), 9.95 (s, 1H).

CLAIMS

- 1 1. Compounds of general formula (I)



(I)

- 2 and their pharmaceutically acceptable salts wherein :
- 3 n is 0 or an integer ranging from 1 to 4
- 4 m is 0 or an integer ranging from 1 to 4
- 5 A is selected from a group consisting of : an acyclic, aromatic or
- 6 heterocyclic residue
- 7 B is selected from the group consisting of : simple chemical bond,
- 8 $-\text{CO}-\text{NH}-\text{CH}(\text{R}_3)-$, $-\text{NH}-\text{CO}-\text{CH}(\text{R}_3)-$ wherein R_3 is H or the side chain of
- 9 a natural alpha-carboxylic acid
- 10 X is selected from the group consisting of : $-\text{NHCO}-$, $-\text{CONH}-$ and
- 11 wherein :
- 12 i) R_1 and R_2 are equal and are selected from the group consisting
- 13 of: oxiranomethyl, 1-aziridinomethyl, C_{2-4} alkyl optionally
- 14 substituted in position 2 with a $-\text{OH}$, C_{2-4} alkoxy, halogen or

15 -OSO₂R₄ group wherein R₄ is selected from the group consisting of
16 C₁₋₄ alkyl or phenyl

17 or

18 ii) R₁ = H and R₂ is as above described

19 provided that :

20 when B = chemical bond, n is different from 1

21 when X = -CONH-, B = simple chemical bond and m = 0 n is different
22 from 0

23 when B = -CO-NH-CH(R₃)- X is different from -NHCO-

24 when B = -NH-CO-CH(R₃)- X is different from -CONH-

1 2. The compounds as claimed in claim 1 wherein:

2 n is as above defined

3 m is zero or an integer comprised between 1 and 3.

4 A = cyclohexyl, p-phenylene, 1-methylpyrrole, thiophene, thiazole,
5 imidazole, furan, isoxazole, oxazole, triazole, pyridine, pyrrole.

6 B is a simple chemical bond, or when it is a -CO-NH-CH(R₃)- group
7 or a -NH-CO-CH(R₃)- group, R₃ is preferably methyl, isobutyl, sec-
8 butyl, hydroxymethyl, mercaptomethyl, carbamoylmethyl, benzyl, 4-
9 hydroxybenzyl, 5-imidazolylmethyl, 2-carbamoylethyl, 2-
10 methylthioethyl, 1-hydroxyethyl, 3-guanidinopropyl, 4-aminobutyl R₁
11 and R₂ represent preferably an ethyl group, 2-hydroxyethyl, 2-
12 chloroethyl, methansulfonylethyl.

1 3. The compounds of formula (I) as claimed in claim 2. selected
2 from the group consisting of:

3 3-[1-Methyl-4-[1-methyl-4-[4-[N,N-bis(2-chloroethyl)amino]benzene-

4 aminocarbonyl]pyrrol-2-carboxyamido]pyrrol-2-carboxyamido]propiona-
5 midine hydrochlorate;
6 3-[1-Methyl-4-[1-methyl-4-[1-methyl-4-[1-methyl-4-[4-[N,N-bis(2-
7 chloroethyl) amino]benzeneaminocarbonyl]-pyrrol-2-carboxyamido]
8 pyrrol-2-carboxyamido]pyrrol-2-carboxyamido]pyrrol-2-carboxyamido]
9 propionamidine hydrochlorate;
10 3-[1-Methyl-4-[1-methyl-4-[1-methyl-4-[1-methyl-4-[1-methyl-4-[4-
11 [N,N-bis(2-chloroethyl) amino]benzeneaminocarbonyl]pyrrol-2-
12 carboxyamido]pyrrol-2-carboxyamido]pyrrol-2-carboxyamido]pyrrol-2-
13 carboxyamido] pyrrol-2-carboxyamido]propionamidine hydrochlorate;
14 3-[1-Methyl-4-[1-methyl-4-[4-[N,N-bis(2-chloroethyl) amino]benzene
15 butanamido]pyrrol-2-carboxyamido]pyrrol-2-carboxyamido]propiona-
16 midine hydrochlorate;
17 3-[1-Methyl-4-[1-methyl-4-[1-methyl-4-[1-methyl-4-[4-[N,N-bis(2-
18 chloroethyl)-amino]benzenebutanamido]pyrrol-2-carboxyamido]pyrrol-
19 2-carboxyamido]pyrrol-2-carboxyamido]pyrrol-2-carboxyamido] propio-
20 namidine hydrochlorate;
21 3-[1-Methyl-4-[1-methyl-4-[1-methyl-4-[1-methyl-4-[1-methyl-4-[N,N-
22 bis(2-chloroethyl) amino]benzenebutanamido]pyrrol-2-carboxyamido]
23 pyrrol-2-carboxyamido]pyrrol-2-carboxyamido] pyrrol-2-carboxyamido]
24 pyrrol-2-carboxyamido]propionamidine hydrochlorate;
25 3-[1-Methyl-4-[1-methyl-4-[4[N,N-bis(2-chloroethyl) amino]benzyl-
26 amino carbonyl]pyrrol-2-carboxyamido]pyrrol-2-carboxyamido]propio-
27 namidine hydrochlorate;

28 3-[1-Methyl-4-[1-methyl-4-[1-methyl-4-[1-methyl-4-[4-[N,N-bis(2
29 chloroethylamino)benzylaminocarbonyl]pyrrol-2-carboxyamido]pyrrol-2-
30 carboxyamido]pyrrol-2-carboxyamido]pyrrol-2-carboxyamido]propiona-
31 midine hydrochlorate;

32 3-[1-Methyl-4-[1-methyl-4-[2-[4-[N,N-bis(2-chloroethyl)amino)
33 phenyl] ethanaminocarbonyl]pyrrol-2-carboxyamido]pyrrol-2-carboxya-
34 mido] propionamidine hydrochlorate;

35 3-[1-Methyl-4-[1-methyl-4-[1-methyl-4-[1-methyl-4-[2-[4-[N,N-bis
36 (2-chloroethyl) amino]phenyl]ethanaminocarbonyl]pyrrol-2-carboxya-
37 mido]pyrrol-2-carboxyamido]pyrrol-2-carboxyamido]pyrrol-2-
38 carboxyamido]propionamidine hydrochlorate;

39 3-[1-Methyl-4-[1-methyl-4-[3-[4-[N,N-bis(2-chloroethyl)amino]
40 phenyl]propylaminocarbonyl]pyrrol-2-carboxyamido]pyrrol-2-carboxya-
41 mido] propionamidine hydrochlorate;

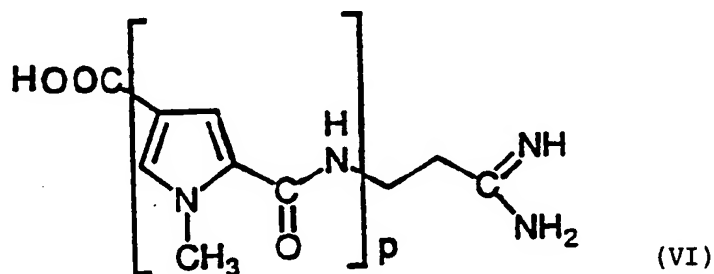
42 3-[1-Methyl-4-[1-methyl-4-[1-methyl-4-[1-methyl-4-[3-[4-[N,N-bis(2-
43 chloroethyl)amino]phenyl]propylaminocarbonyl]pyrrol-2-
44 carboxyamido]pyrrol-2-carboxyamido]pyrrol-2-carboxyamido]pyrrol-2-
45 carboxyamido] propionamidine hydrochlorate;

46 3-[1-methyl-4-[1-methyl-4-[1-methyl-4-[1-methyl-4-[1-methyl-4-[3-
47 [4-[N,N-bis(2-chloroethyl)amino]phenyl]propylaminocarbonyl]pyrrol-
48 2-carboxyamido]pyrrol-2-carboxyamido]pyrrol-2-carboxyamido]pyrrol-2-
49 carboxyamido]pyrrol-2-carboxyamido]propionamidine hydrochlorate;

50 3-[1-Methyl-4-[1-methyl-4-[4-[N,N-bis(2-chloroethyl)amino]benzyl
51 carboxyamido]pyrrol-2-carboxyamido]pyrrol-2-carboxyamido]propio-
52 namidine hydrochlorate;

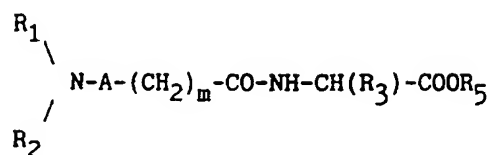
- 53 3-[1-Methyl-4-[1-methyl-4-[1-methyl-4-[1-methyl-4-[4-[N,N-bis(2-
54 chloroethyl)amino]benzylcarboxyamido]pyrrol-2-carboxyamido]pyrrol-
55 2-carboxyamido]pyrrol-2-carboxyamido]pyrrol-2-carboxyamido]
56 propionamidine hydrochlorate;
57 3-[1-Methyl-4-[1-methyl-4-[2-[4-[N,N-bis(2-chloroethyl)amino]
58 phenyl]ethylcarboxyamido]pyrrol-2-carboxyamido]pyrrol-2-carboxy-
59 amido]propionamidine hydrochlorate;
60 3-[1-Methyl-4-[1-methyl-4-[1-methyl-4-[1-methyl-4-[2-[4-[N,N-bis
61 (2-chloroethyl)amino]phenyl]ethylcarboxyamido]pyrrol-2-
62 carboxyamido]pyrrol-2-carboxyamido]pyrrol-2-carboxyamido]pyrrol-2-
63 carboxyamido]propionamidine hydrochlorate;
64 3-[1-Methyl-4-[1-methyl-4-[1-methyl-4-[N,a-[4-[N,N-bis(2-chloro-
65 ethyl)amino]benzoyl]glycylamino]pyrrol-2-carboxyamido]pyrrol-2-
66 carboxyamido]pyrrol-2-carboxyamido]propionamidine hydrochlorate;
67 3-[1-Methyl-4-[1-methyl-4-[1-methyl-4-[1-methyl-4-[N,a-[4-[N,N-
68 bis(2-chloroethyl)amino]benzoyl]glycylamino]-pyrrol-2-
69 carboxyamido]pyrrol-2-carboxyamido]pyrrol-2-carboxyamido]pyrrol-2-
70 carboxyamido]propionamidine hydrochlorate;

1 4. Compounds of formula (VI)



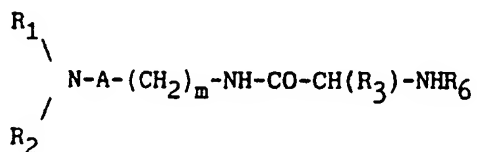
2 wherein p is an integer comprised between 3 and 6.

1 5. Compounds of formula (IX)



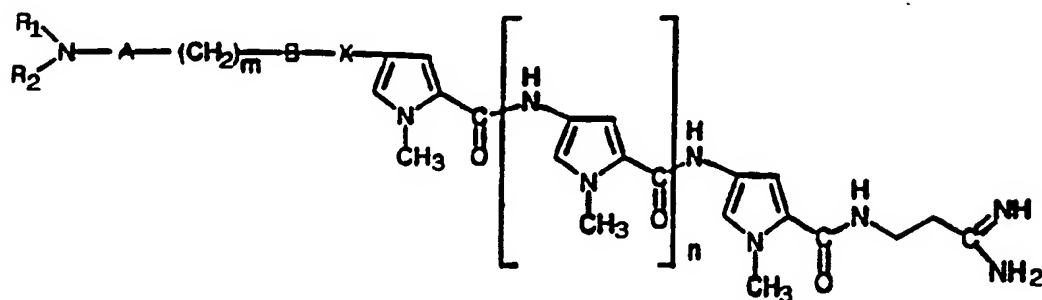
2 wherein A, m, R₁, R₂, R₃ and R₅ are as claimed in claims 1) and 2).

1 6. Compounds of formula (XII)



2 wherein A, m, R₁, R₂, R₃ and R₆ are as claimed in claims 1) and 2).

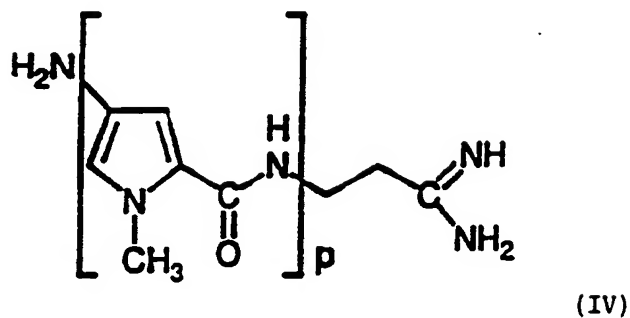
1 7. A process for the preparation of compounds of formula (I)



(I)

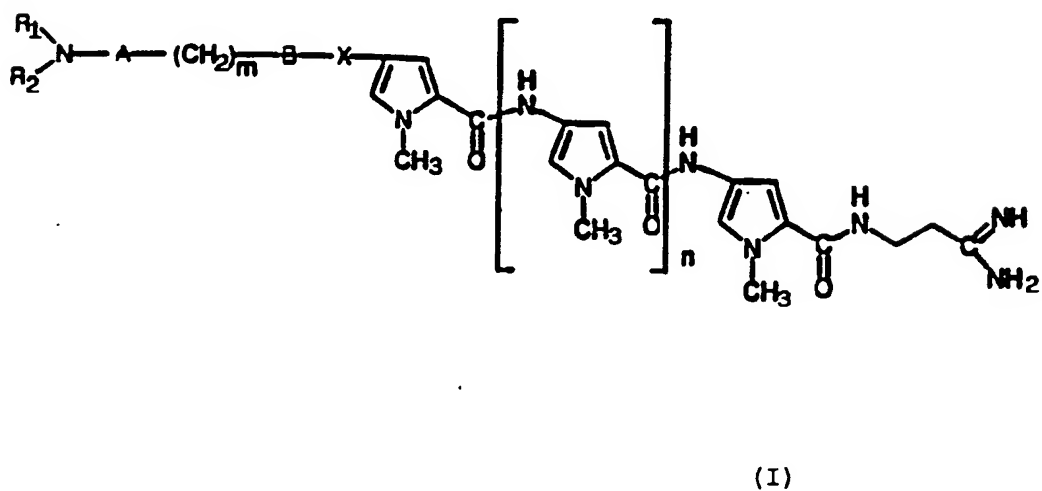
- 2 wherein:
- 3 n is 0 or an integer ranging from 1 to 4
- 4 m is 0 or an integer ranging from 1 to 4
- 5 A is selected from the group consisting of : an acyclic, aromatic
- 6 or heterocyclic residue.
- 7 B is selected from the group consisting of : simple chemical bond,
- 8 -CO-NH-CH(R₃)-, -NH-CO-CH(R₃)- wherein R₃ is H or the side chain of
- 9 a natural alpha-carboxylic acid
- 10 X is selected from the group consisting of : -NHCO-, -CONH- and
- 11 wherein :
- 12 i) R₁ and R₂ are equal and are selected from the group consisting
- 13 of: oxiranomethyl, 1-aziridinomethyl, C₂₋₄ alkyl optionally
- 14 substituted in position 2 with a OH, C₂₋₄ alkoxy, halogen or
- 15 -OSO₂R₄ group wherein R₄ is selected from the group consisting of
- 16 C₁₋₄ alkyl or phenyl
- 17 or
- 18 ii) R₁ = H and R₂ is as above described
- 19 provided that :
- 20 when B = chemical bond, n is different from 1
- 21 when X = -CONH-, B = simple chemical bond and m = 0, n is different
- 22 from 0
- 23 when B = -CO-NH-CH(R₃)- X is different from -NHCO-
- 24 when B = -NH-CO-CH(R₃)- X is different from -CONH-
- 25 comprising reacting the compound of formula (III), wherein A, m, B,

26 R_1 and R_2 are as above defined, with a compound of formula (IV)



27 wherein p is an integer comprised between 2 and 6.

1 8. A process for the preparation of compounds of formula (I)



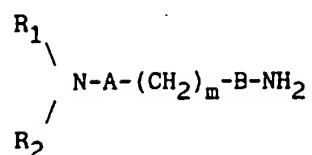
2 wherein:

3 B is a simple chemical bond or a $-NH-CO-CH(R_3)-$ group, X is the

4 $-NHCO-$ group and m , n , R_1 , R_2 and R_3 are as claimed in claim 7).

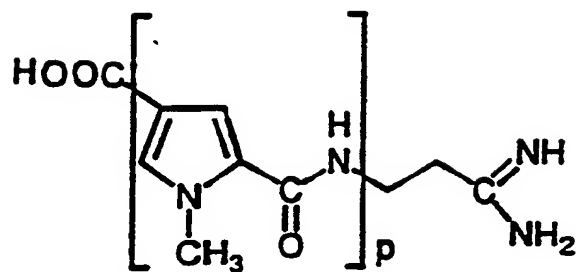
5 provided that, if B is a chemical bond n is different from 1;

6 comprising reacting the compound of formula (V)



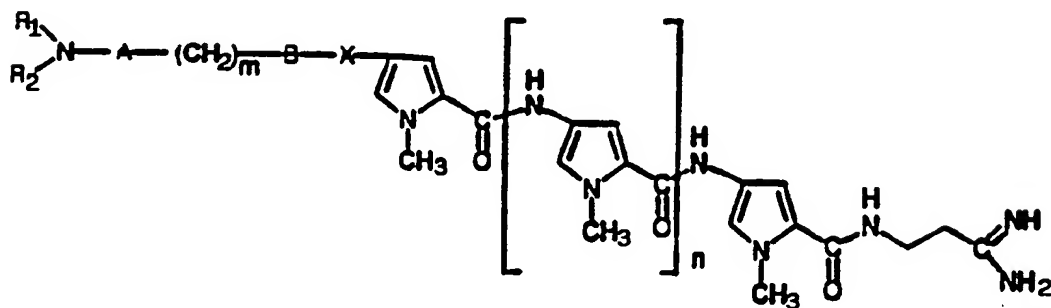
(V)

7 wherein A, B, m, R₁ and R₂ are as above defined, with a compound of
8 formula (VI)



9 wherein p is an integer comprised between 2 and 6.

1 9. A process for the preparation of the compounds of formula (I)



2 wherein:

3 B is a simple chemical bond

4 X represent the -NHCO- group or the -CONH- group and m, n, A, R₁

5 and R₂ are defined in claim 7),

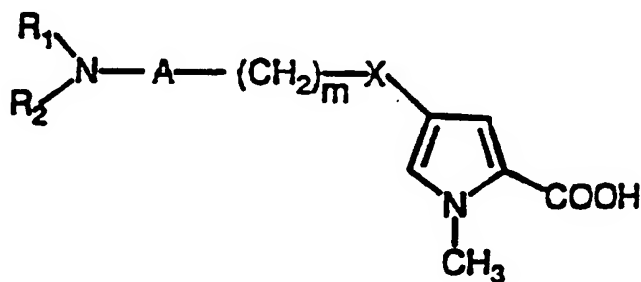
6 provided that:

7 if B is a chemical bond, n is different from 1;

8 if X is -CONH- and contemporaneously B is a chemical bond and m is

9 equal to zero, n is different from zero;

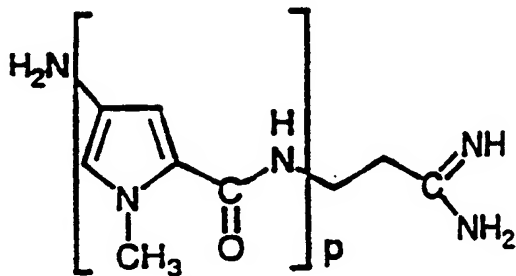
10 comprising reacting the compound of formula (VII)



(VII)

11 wherein A, X, m, R₁ and R₂ are as above defined, with a compound of

12 formula (IV)



(IV)

13 wherein p is an integer comprised between 1 and 5.

1 10. Use of compounds as claimed in claims 1-3 for the preparation
2 of pharmaceutical compositions.

1 11. Pharmaceutical compositions containing as active principle a
2 compound as claimed in claim 1 in combination with a
3 pharmaceutically acceptable vehicle or diluent.

1 12. The pharmaceutical compositions as claimed in claim 11 as
2 antitumoral agents. 13. The pharmaceutical compositions as claimed
3 in claim 11 as antiviral agents.

1 14. A therapeutic method for the treatment of tumoral affections
2 comprising administering to patients, from 1 to 4 times a day,
3 pharmaceutical compositions containing as active ingredient a
4 compound as claimed in claim 1, in an amount ranging from 0.1 to
5 100 mg per unitary dose in a pharmaceutically acceptable diluent or
6 vehicle.

1 15. A therapeutic method for the treatment of viral affections
2 comprising administering to patients, from 1 to 4 times a day,
3 pharmaceutical compositions containing as active ingredient a
4 compound as claimed in claim 1, in an amount ranging from 0.1 to
5 100 mg per unitary dose in a pharmaceutically acceptable diluent or
6 vehicle.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 94/00557

A. CLASSIFICATION OF SUBJECT MATTER

IPC 5 C07D207/34 A61K31/40 C07C237/10 C07C237/20 C07C237/36

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 5 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, X	WO, A, 93 13739 (MENARINI) 22 July 1993 see for example RN 150691-41-11 ---	1-4, 7-15
A	EP, A, 0 388 948 (CARLO ERBA) 26 September 1990 see for example RN 132244-93-0 and 132244-97-4 ---	1-4, 7-15
A	EP, A, 0 246 868 (CARLO ERBA) 25 November 1987 see for example RN 115309-01-8 and 115309-02-9 --- -/--	1-4, 7-15



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date, claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of the international search

18 July 1994

Date of mailing of the international search report

22. 07. 94

Name and mailing address of the ISA

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Authorized officer

Kissler, B

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 94/00557

C(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	BIOCHEM. PHARMACOLOG. vol. 45, no. 7 , 1993 pages 1536 - 1539 Montecucco, Alessandra; Lestingi, Marta; Rossignol, Jean Michel; Elder, Rhoderick H.; Ciarrocchi, Giovanni 'Lack of discrimination between DNA ligases I and III by two classes of inhibitors, anthracyclines and distamycins' see for example RN 149127-31-1 ---	1-4,7-15
A	JOURNAL OF MEDICINAL CHEMISTRY. vol. 32, no. 4 , 1989 , WASHINGTON US pages 774 - 778 Arcamone, Federico Maria; Animati, Fabio; Barbieri, Brunella; Configliacchi, Emanuela; D'Alessio, Roberto; Geroni, Cristina; Giuli 'Synthesis, DNA-binding properties, and antitumor activity of novel distamycin derivatives' see the whole document ---	1-4,7-15
A	ANTI-CANCER DRUG DES. vol. 1, no. 3 , 1986 pages 235 - 244 Arcamone, F.; Lazzari, E.; Menozzi, M.; Soranzo, C.; Verini, M. A. 'Synthesis, DNA binding and antiviral activity of distamycin analogs containing different heterocyclic moieties' see for example RN 106575-22-8 -----	1-4,7-15

INTERNATIONAL SEARCH REPORT

International application No.

PCT/EP 94/00557

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 14-15 are directed to a method of treatment of (diagnostic method practised on) the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
Claims search incompletely: 1,2,7-15
Claims not searched : 5,6

Please see attached sheet ./.
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.☐ No protest accompanied the payment of additional search fees.

precludes even a partial structure search.

The definition of the following substituent(s) is too general and/or encompasses too broad a range of totally different chemical groups, only partly supported by examples given in the descriptive part of the application:

A : acyclic, aromatic, heterocyclic

The number of theoretically conceivable compounds resulting from the combination of all claimed substituents of above list precludes a comprehensive search. Guided by the spirit of the application and the inventive concept as disclosed in the descriptive part of the present application the search has been limited to the following case(s):

A is o-phenylene, m-phenylene or p-phenylene (claims 1-3,7-15)

(Cf. Arts. 6, 15 and Rule 33 PCT, Guidelines Exam. Part B, Chapt. III, 3.6, 3.7)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/EP 94/00557

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO-A-9313739	22-07-93	NONE	
EP-A-0388948	26-09-90	AU-B- 635733	01-04-93
		AU-A- 5276190	22-10-90
		DE-D- 69005164	27-01-94
		DE-T- 69005164	31-03-94
		WO-A- 9011277	04-10-90
		EP-A- 0416075	13-03-91
		JP-T- 3504863	24-10-91
		US-A- 5175182	29-12-92
EP-A-0246868	25-11-87	AU-B- 597659	07-06-90
		AU-A- 7316387	26-11-87
		CA-A- 1314551	16-03-93
		DE-A- 3781716	22-10-92
		JP-B- 6023193	30-03-94
		JP-A- 62294653	22-12-87
		SU-A- 1528316	07-12-89
		US-A- 5017599	21-05-91
		US-A- 5049579	17-09-91
		US-A- 5310752	10-05-94
		ZA-A- 8703593	12-11-87